February 5th, 2024 Patient Education Webinar Transcript- Pemphigus Overview

Becky Strong: Welcome everyone. This webinar is now being recorded. I am Becky Strong, IPPF Outreach Director, and I'll be your host for today's webinar. My voice is kind of coming and going, and so I will apologize ahead of time. But I would like to thank all of you for being on the call with us today. Before I start the webinar, “I want to remind everyone that information is key in treating and living with any condition. However, everybody's situation is unique. So the IPPF reminds you that any information found online or during presentations like this one should be discussed with your doctor or healthcare team to determine if it applies for your situation.” Today we are excited to have Dr. Kyle Amber with us to discuss a disease overview of pemphigus. So let me introduce you to our speaker. Dr. Kyle Amber is an international leader in the field of autoimmune blistering diseases as well as complex dermatology. He has published over 100 peer reviewed manuscripts as well as numerous book chapters pertaining to the diagnosis and treatment of autoimmune blistering diseases. He created Chicago's first dermatology infusion center at Rush University, providing care for patients with blistering diseases, hidradenitis suppurativa and other conditions requiring intravenous therapies. His research lab focuses on mechanisms of innate immune activation in pemphigoid, with a particular interest in single-cell transcriptomic approaches. His work aims to identify treatment targets that can reduce or eliminate the need for high-dose corticosteroids during the acute phase of disease. Now before I begin I would like to review a few housekeeping items… (Reviews Housekeeping slides). Now it is my pleasure to hand it over to Dr. Amber.

Dr. Kyle Amber: Thank you, Becky. Nice to be with everybody today. I'm glad to not make you talk any more than you have to already. So let me share my screen here, and then I will also turn off my video so I don't see a little me in the corner that's not pleasant to watch. So today I'll basically be talking about an introduction to pemphigus. The way I sort of like to do this is, I think fundamentally the immunology of the disease and what you see in the clinic are very much matched. I don't expect this to be an in depth discussion of immunology, but at the same point of time when you understand the basics it really helps figure out, why is this happening in the disease? Why is this not happening? Why do I need this treatment and why does this treatment not work at this point in time, etc?

Dr. Kyle Amber: So we'll sort of dive in there. It's really to sort of translate what's going on in the body to what's going on with the patient so then we can sort of figure out what's going on and how do we pick the best treatments for people?

Dr. Kyle Amber: So I start with basically, what is immunoglobulin? This is basically another name for this is called antibodies. We have tons of antibodies in our body. They serve an important role in terms of protection. They are what protect you from bacteria, fungus, viruses, etc. This is just one of many mechanisms in the body to protect yourself. The problem is, sometimes they don't do what they're supposed to do. We're not supposed to attack ourselves but when they do, they're called autoantibodies. So why does it matter? And I'll try to highlight this, why it matters, during a lot of this. Treating autoimmune disease is really a double edged sword. If you remove all the antibodies in the human body, fantastic, there will probably be no pemphigus, except now you have no immune system. That's the thing that's keeping you safe. That's the big challenge in treating these diseases, fix one thing without making everything worse.

Dr. Kyle Amber: Then, what makes immunoglobulin? This is going to be related to B cells. When we talk about Rituxan and treatments, etc. we bring up B cells, T cells, all of these things. And so again, where this becomes important is, this is the maturation of B cells, so how B cells grow up over time. You can see that the ones that actually secrete the antibodies are these plasmablasts and plasma cells and Rituxan does not work on those. Rituxan works earlier in the phase of things. We are basically killing the replacement cells that make these antibodies.

Dr. Kyle Amber: What causes pemphigus is basically antibodies target normal proteins in the skin. In general, the average healthy person should not have these. These are primarily thought to be against proteins called desmoglein 1 and desmoglein 3. Desmoglein 1 being the more key protein and pemphigus foliaceus and desmoglein 3 being the more key protein in pemphigus vulgaris. Then patients with pemphigus vulgaris with both oral and skin disease tend to have both. But that is a simplified approach. There are numerous other proteins that are described in patients with pemphigus, and this is where it gets a little clinically tricky. You can have patients who have pemphigus, who, when you check for desmoglein antibodies they are totally negative. In the era of trying to come up with targeted therapies that only target desmoglein antibodies, are we really covering everything? So those are sort of a little bit of limitations. Another concept that comes up is something called epitope spreading. This ties into when you basically are immune to one thing and become immune to multiple things. Basically what this means is if you have immunity to one little area of desmoglein, as you have more immunity over time, you start to get immunity to multiple areas of desmoglein and some areas of desmoglein are more important than others for the purposes of causing disease. Likewise, in mucocutaneous pemphigus where patients have oral disease then it goes to the skin, it's thought that basically you go from attacking desmoglein 3 and now, oops the body sort of lost track of things and now it's targeting desmoglein 1. Where it becomes important is in patients

with more prolonged diseases. I think of things in terms of autoimmune memory. How much does your body want to attack itself? In the very early phases of disease, the body is not really convinced. It's toying around with the idea of autoimmune disease. In a patient who's had the disease for 30 years, it's really quite ingrained to attack.

Dr. Kyle Amber: So what causes pemphigus? Basically antibodies disturb the skin and mucus in several ways. You have these antibodies that attack these proteins in the skin, and that causes the cells to basically fragment and die. There is not a lot of inflammation going on. So basically, the skin shrivels up. But if you look under a microscope, you don't see tons of inflammation as you do in other diseases like pemphigoid for example. These antibodies can also block the cells from binding to each other but also they cause this active signaling process. And that's why steroids typically don't work in low doses. In pemphigus we have to use extremely high doses of steroids and that's because we're really targeting that very last step of the skin cells fragmenting. We're not targeting some inflammation, etc. which is generally pretty responsive, and that makes things a bit more challenging.

Dr. Kyle Amber: Now, how does this translate clinically? It translates to exactly what we see. So the absence of inflammation is a huge clinical clue to pemphigus. So I try not to put a bunch of pictures in here, because this is a patient education webinar and unfortunately most of you are probably aware of these things. But this one I like to really point out, because multiple things can happen in the same person. This is sort of the standard clinical differential we build. Somebody has an ulcer in the mouth, what is it? When you look on the left, in pemphigus you really don't see any inflammation, you see this ulcer but on the border there's nothing. Compare that to an aphthous stomatitis, which is a canker sore, tons of red in the border, and it's nice and round. Then herpetic stomatitis, which is basically a herpes infection of the gum again, very, very bright red around here. That's really your clinical clue and it translates to exactly what you're seeing going on underneath the microscope. Basically, these cells are fragmenting but there's no inflammation involved in the picture. I also put this here because patients can have pemphigus and canker sores too which is important for just the eyeball test. The eyeball test is what does it look like? If it is intensely red, then it's unlikely to be pemphigus. Obviously it can happen as these diseases don't read the book, but that's how we sort of weigh things.

Dr. Kyle Amber: So diagnosis, this is sort of a busy slide. What do we do to basically call it what it is? The important thing is the clinical presentation obviously. Generally speaking, these blisters don't just come and go immediately. Maybe in the very early phases there may be a little of that, but these tend to be chronic conditions, not just something that pops up. There's 2 different biopsy techniques and distinguishing this is very, very important. So the traditional one is basically how we diagnose everything in dermatology and most diseases. You take a sample,

you put it in a preservative, you look under a slide, and you say it looks like this. You can definitely see signs that are suggestive of pemphigus but there's tons of stuff that can mimic this and that on its own is not enough. There's a special biopsy technique called direct immunofluorescence, which basically looks at those antibodies we were talking about and you see them all deposited on the skin. So if you have a patient who clinically has a blister, and you see tons of antibodies on the skin, it sort of tells you they must have the blister or this erosion because they have these antibodies. An important thing is, this is not unfortunately performed super routinely as it should. So not all dermatologists, oral surgeons, ENT (ear, nose, throat) dentists, etc., have the setup. You need to have a special bottle for this type of thing. While it should be routinely done to do this, unfortunately in the real world if you only see one of these every couple of years, is it worth maintaining the bottle and getting a new one every year? A lot of practices say, we'll just do the first test. The first test can give you a clue but unfortunately, that also really delays diagnosis. If the test reads negative, people assume well, it can't be pemphigus. Or it's positive, and then it's called pemphigus but it's really something else. So that second test is quite important. The other thing is site selection is really important. As a dermatologist this is also true and really in any field where you're taking a biopsy, you are taking a little tiny sample and assuming that what you took is representative of everything going on in the whole person. Unfortunately the site selection is important. The logical choice, you have an active blister, let me take the active blister to show me what's going on. No, you lose some of the material so you try to go for something adjacent. A lot of times if somebody isn't super experienced with these techniques and they take a bad sample. If you get a negative result, they say, it can't be pemphigus, I got a negative result. Then I redo it one centimeter away from where they took it and boom it’s pemphigus and it’s clear as day.

Dr. Kyle Amber: Blood tests can also be quite useful and the guidelines for diagnosis are really based on having that positive direct immunofluorescence and I think in principle that's true. But I also am a bit empathetic when somebody's been biopsied five times and they're all negative but it looks clinically like pemphigus, is there another way we can do it without just biopsying them over and over again? And this is where blood work is quite helpful. There's a few different types of tests. Indirect immunofluorescence is basically when you take a slide with normal skin and you put the patient's blood on it. If the patient's blood reacts with the skin, you say okay, they clearly have antibodies against the skin. If you dilute it over and over and over again, and the more you dilute it if you still see a signal, it tells you that the patient really has a lot of antibodies to the skin targeting that area. Whereas you dilute it once it's gone, it was a pretty low signal. That's going to give you the big picture. It tells you basically the patient's blood is reacting with skin. It doesn't tell you, it's reacting with desmoglein or with this protein but it tells you overall. So this is sort of a helpful screening test because again, the big picture. Now desmoglein ELISA

is a little fragment of that protein we were talking about and basically similar concept, you add the patient's blood to a little dish with desmoglein on it and it shows you how much of the blood reacts with desmoglein. The differences between these tests though are, these desmoglein ELISA's are much easier to get. They're commercial tests available, most routine labs that you go to will be able to do them. And the other thing that I like about those is that there is no potential for user error. So no one is reading a slide or trying to interpret these things. It's basically, this is the number and it is what it is as long as the thing is calibrated. Whereas in indirective immunofluorescence, someone's looking at it and saying, I think that signal's gone when I diluted it 400 times. And that's important because a lot of times, unfortunately some insurances require you to send to one lab or another. There's certain ones that just frankly, I don't trust the results but if you send it to another place with a lot of experience and then all of a sudden you get the read that you expected and there shouldn't be a discrepancy but there is. The point is there's a whole bunch of ways to get to the same thing. Somebody with sky-high antibodies to desmoglein, it looks like pemphigus but has had a negative biopsy, I really don't belabor the point. Whereas somebody with low levels who may have had a negative biopsy, sometimes there's a role of rebiopsying. While the gold standard is do all of these things, I do think common sense has to prevail. But point is there's a lot of different ways to get to the same answer and we try to use all those tools to get it right.

Dr. Kyle Amber: So one thing I always like to highlight is some of these tests like we were talking about are subjective, some of them are objective. This is a subjective test, so this is what a direct immunofluorescence looks like. You take a biopsy, on the left is pemphigus, on the right is pemphigoid, you stain it and you see these beautiful depositions. The textbook shows this, our textbooks show that. We don't get a ton of routine training and reading these things in dermatology but people who do specialized training get it. But if you don't see it all the time, your expectation is it looks like this. The reality is you get this, it's mush. You see this green stuff and it is really not quite clear, is it positive, is it negative, is it highlighted? Because as you see, normal skin already has these. That's an important thing, not every positive biopsy I get do I believe. Likewise, not every negative biopsy result do I believe. You have to know who's reading it, what location was it taken from. So there's unfortunately a subjective element which can sometimes delay diagnoses or make people falsely call it a negative biopsy or a positive biopsy and make decisions there.

Dr. Kyle Amber: Moving a little bit to sort of why did pemphigus happen? We know there's genetic risk factors for it and the common question I get is will my relative get this? The important thing to remember is just because you have the genetic risk factor in no way means there's a significant impact. So we can talk about statistical significance where I can do a study and show there's a two time increased risk. But the way I view it is as follows, if I say you have a

four in a million chance of getting pemphigus and you have a genetic risk factor that makes you three times more likely, your relative's risk is now 12 in a million. There are 1-5% of people in the population walking around with that same gene. So clearly the gene plays a very small role even though it has some role. The environment, the experiences in life all play a huge role. There's one studied subgroup of this in Brazil where they've really shown the interaction between environment and genetics where basically 55% of people in this population have antibodies to desmoglein. But they're not harmful, they're not pathogenic. After they get bitten by a black fly the body's immune system gets and it starts to attack a different part of the same protein. A little switch in the immune changes and boom, now these people are having pemphigus foliaceus at a very high rate. This is just one very well studied example and for some reason this has come up on Google so much higher lately because everybody with pemphigus foliaceus asks if they've been bitten by a black fly, highly unlikely. This is just in one region, the interaction between genetics and environmental risk factors. The way I think of it is so many things have to go wrong in autoimmunity and a genetic risk factor such as if you got sick at this time of the day, then got this sickness, then started this medication seven days after that. All of those things have an effect on the immune system and it becomes very difficult to go backwards and say, oh, this was the one thing that did it. It's just not unfortunately as simple as that. And because of that, genetic testing is not performed for pemphigus. Even if it told you you had a high risk gene, like I said, then your risk would be twelve in a million instead of four in a million and that still doesn't really explain anything in terms of why it happened.

Dr. Kyle Amber: Demographics, so the incidents can range from anywhere to 0.1 to 2.7 people per a hundred thousand per year. They're higher rates are documented in certain populations, especially in the Ashkenazi Jewish population, inhabitants of India, southeast Europe and the Middle East. The average age of onset is usually between 40 to 60 years of age, fairly rare in children, but keep in mind these are average ages. Somebody's got to make the bell curve. I've seen it as young as nine years old and I don't specialize in pediatrics, so I have no doubt it's going to be in younger populations, all the way to 85 plus year olds for pemphigus. Whereas with pemphigoid, we see upwards even above a 100 years old. So that's just the average, but take the average with a grain of salt.

Dr. Kyle Amber: We convert things now to goals of treating autoimmunity and alluded to it a little bit is basically stop making bad antibodies but still make good antibodies. In principle that way you are not getting rid of your natural immune system, but you're not attacking yourself. That's the goal. Obviously it's a little trickier, easier said than done.

Dr. Kyle Amber: I like to divide treatment time points in pemphigus because there's different things that we do at different points of the disease because they all work at different speeds. With acute treatments, I think what can I do to get the treatment to get the disease under control within a couple of weeks? Essentially you have blisters, you don't want to have blisters anymore in the short term, what do you do? Unfortunately there's not a lot of good options. I mean prior to steroids, pemphigus was essentially fatal. Now it's just a matter of managing steroids, using steroids-sparing agents, et cetera. There's not a great shortcut out of high dose steroids when things are going badly. You can use doxycycline. I use it uniformly because it works in all of them to a degree in terms of sparing steroid dose, but on its own not the strongest thing. IVIg is another treatment that's basically healthy patients antibodies, but these things are much less potent than steroids. So if you did all of those things and no steroids, you probably wouldn't notice really much going on. It just allows you to save maybe 20 milligrams worth of steroids. At the right dose, and I say right is whatever individual response you should see lesions drying up by about three weeks. There are these chronic mouth, scalp and sometimes nose lesions which can take longer. In a way we kind of, I don't want to say ignore them or pretend they don't exist, but you don't necessarily have to blast someone with a high dose of steroids for one stubborn lesion that's been there for years. You can do injections, other things like that. So once you hit that gold dose, things really dry up by about three weeks. Sometimes you need just another couple if things are going slowly or you say, oh nope, that's not the right dose, I need to go higher and then things dry up, then you can start tapering down. A couple notes is, you need several weeks. The turnaround time is unfortunately not faster than that, even though some people may notice some improvement within a week. For me, three weeks is that time that I know this is the right dose or I need a higher dose. Sooner, I just don't have much luck with. Another thing is low doses and quick tapers are almost guaranteed to fail. Unfortunately, most patients have had the experience of going to the emergency room, urgent care, primary care or dermatologist gets a week or two weeks of steroids, maybe it helps for a few days tapers off, everything is right back to where you started. The principle I really try to stick to is basically doing it right, do it once, and never do it again. My goal is to use the right amount of steroids to get things under control as quickly as possible, no more than necessary and no less, to expedite getting a patient off of steroids. Minimize the entire exposure of steroids over a patient's lifespan or especially the span of that disease flare rather than starting somebody on a suboptimal dose, nope, they're not well now we have to go up. Oh nope, they're still not well so we go up and we just keep the steroids going and not get to where you need to go. So remember, we're targeting the skins shriveling up. We're not removing the antibodies, your body is still making those. Even if we get things perfectly clear with steroids, it's still not really addressing the underlying problem of the body's trying to attack itself. So what do we do next?

Dr. Kyle Amber: The other treatment time point is going to be chronic treatments. Basically I think this is what can I do to get you off of steroids? Great, three weeks you're cleared up on steroids, you hate my guts because you're on 80 milligrams or a very high dose and have the side effects for it. What can I do to expedite that and not just have the disease come right back? These are much better options. The safety side effect profile and the toleration of them is much better. They are incredibly slow. Rituximab we'll talk about more, is an FDA approved therapy, but it really takes about seven months to reach peak effect. So the way I think of it is if somebody is in the say mild to moderate disease spectrum, I start them on Rituximab and I say, you're eating okay, you're living your life. Now it's a question, do you want 80 milligrams of prednisone to be cleared up and to taper that over six months or you want to try to hold off and we're not always able to do that unfortunately, but in the cases you can, it's great. The problem is it takes seven months. You're sitting there waiting, you're like, okay, I hope things are going to heal soon. And eventually you reach that point, but it is quite slow. Oral immunosuppressants such as Mycophenolate, Azathioprine, et cetera, these are generally an onset of two to three months, but these are much less potent. There's a nice study comparing Mycophenolate to Rituximab. Mycophenolate is much less effective. So in my opinion, unless there's some major medical issue with Rituximab and even then we still have other options, I really don't believe there's much of a rationale in starting with these. Unfortunately, it's much more convenient. It doesn't require an IV infusion and coordinating IV infusions is just not a very pleasant thing to do in outpatient medicine. Unfortunately, a lot of times I see patients who get started on mycophenolate, they taper down on their steroids, they still can't get off and then they're just in limbo on Mycophenolate on a low dose of steroids and had they gotten Rituximab, they would've been better already by that time point. So thankfully there was that nice clinical trial that showed that. I hope that people will move away from sort of doing just convenience in the sake of avoiding the logistical headaches, but it really isn't effective. The other chronic treatment is IVIg, that's the high doses of antibodies from healthy individuals. The way to think about it is, I'm just trying to water down the bad antibodies. Let's say you have a hundred antibodies in your body, 90 good ones, 10 bad ones. If I give you a million antibodies from healthy people, your body becomes overwhelmed and then says, I've got to get rid of this excess antibodies. Let me just start recycling, getting rid of it. So I keep giving you good stuff and making the bad stuff, but eventually you just keep selectively rid of the bad stuff. So the safety profile is quite good. It's not immunosuppressive. There is a risk of blood clots and headaches, but still fairly on the low side. Unfortunately it's just not really strong enough on its own and there's also what's considered a rebound phenomenon. So if I give you these million antibodies from healthy people, you get rid of your 10 antibodies, next month your body tries to make 20 to compensate

for it. If I don't give you another dose of IVIg, now you have twice as bad disease as you had before. So it's usually paired up with something else to increase the speed of response and have that non immunosuppressive aspect that you can add on to things.

Dr. Kyle Amber: It took me forever to draw out this curve. I am a half Italian American and cannot help but speak with my hands. I feel like half the time I'm drawing these imaginary curves in front of patients, and I really feel like I need a whiteboard. So it was so important to me with this talk to draw out what I always say. This balancing act of acute and chronic treatment. The idea here is that, this is without steroid sparing treatments. You start a patient on a high dose of steroids and their disease is doing better so you keep tapering it down and all of a sudden you hit a wall. Say you started the patient on 80 milligrams, you drop in the 40 to 30 and then boom, you hit 20 and there's a flare. You go back up to 30, it's good, you go back down to 20 then a flare. That basically tells you you are stuck at 30. And prior to the era of these steroid-sparing drugs, we would sort of pat ourselves on the back and say, great, we have the disease under control on a lower dose of steroids than before. That's not ideal. But that's the natural course of this disease. The problem is it is pretty much impossible to put somebody on steroids and expect to get them off of steroids without doing anything else. And even if that is the case, which is really only a small percentage of patients, that can take somewhere around the two year mark. Whereas when you use a steroid-sparing treatment, that can be in the six-ish months. So now we look at the second curve. Basically the same thing. The steroid dose is coming down. Great, we cleared up the disease, the dose keeps going down. Previously you would've hit that wall right around my cursor where the blue arrow is. Now the red arrow is your steroid sparing drug and this basically means, okay, now let's take Rituximab, it takes seven months to kick in fully, but by three months it's doing something. That may have been where I hit the wall with steroid dosing and now all of a sudden instead of my patient getting stuck at 30 milligrams, I can just keep chugging along and tapering off the steroid dose almost always faster than had I not had the steroid-sparing drug in general. It's where these curves kind of meet, that's when you can really start pushing the dose down and where these steroids sparing drugs make a difference. Unfortunately, a common thing is, you can give Rituximab to someone with bad disease and unfortunately there's this expectation that within a few weeks it'll do something. It pretty much never does something that quickly in my experience at least. In which case it doesn't change the fact that you still need that initial high dose.

Dr. Kyle Amber: So I alluded a little bit to stubborn lesions and these ones are frustrating. In longstanding disease with aggressive lesions, patients can get these chronic spots. Mouths, nose, scalpes are really going to be the more common area, sometimes groin fold as well.

Interestingly, biopsies of these spots have basically shown there's a little mini immune system inside the skin that seems to act independently. So it's not as simple as, let me give a hundred doses of Rituxan and I will finally get rid of that small one. That may happen eventually, but the rest of the patient will be totally fine, there will just be that one spot. You don't want to just leave it there because eventually that can trigger a relapse but we have to address these ones a little bit differently. These can respond with injections and local therapy. Usually a steroid injection and sometimes they'll do an injection of Rituximab into that spot itself. These really don't always require aggressive therapy. So if I'm smoothly tapering somebody off of steroids and that one stubborn spot is just completely unchanged, that doesn't mean I have to pump the dose all the way back up and cause all the side effects that go along with it. I can sort of deal with it independently and wait it out and generally things go well.

Dr. Kyle Amber: Another definition we use is something called transient lesions. These are lesions usually responding in less than 72 hours. Generally somebody's on treatment, they drop the dose of steroids and oh no, I got two little tiny blisters, but they went away within 24 hours. We don't really worry about these that much. These can occur despite really good disease control and they actually don't tie to worse prognosis. I always want to know about them, but at the same point in time, I'm generally not alarmed. I mean if it's happening every single day with an increased frequency, I'm going to be a little bit hesitant to start tapering therapy more aggressively. But the general course of just a little flare up here or there that spontaneously resolves, generally we essentially kind of ignore it and then taper as we would have normally.

Dr. Kyle Amber: I put treatment strategies on here. There's really a couple. Remission on therapy is great. We want to clear up the disease. We get to moderate to low doses of steroids on an immunosuppressant and we say, great, the disease is clear now that we are on these medications, let's just continue that. The other strategy is remission on minimal therapy. We want to be on a really low dose of steroids or just maintenance on immunosuppression. Then the other one is remission off of therapy, which basically you want the disease gone and you want to be off of all medications. Obviously the last one is the goal. It's not always possible, but that's what we aim for. Whereas the top one, remission on therapy used to be more acceptable and really I'd like to think we're much better off than that. It always bothered me for example, in the Japanese treatment guidelines, they sort of say the end goal is getting a patient to 7.5milligrams of prednisone and immunosuppressants and they say, great, that's a great outcome. And 20 years ago that may have been true, but I do think we're better than that nowadays. It's basically a matter of can we keep a patient clear on medication or can we keep a patient clear off of medication, not this low dose steroids or having the disease not well

controlled. Remission off therapy, it is easier with newer diagnoses. A patient who's had a disease less than five years, especially less than two years, as I mentioned I always think of it as the immune system is flirting with the idea of really attacking itself, it's not longstanding. A great example of this is when you give a patient Rituximab, their desmoglein antibodies will usually go away. But if you look at childhood vaccinations, those levels remain completely unchanged. The hard wiring of the immune system is different for long standing disease and shorter standing disease, which means it's more stubborn. Not to say we can't get longstanding disease under better control if somebody's 20 years out, still on steroids still on something. There's definitely ways we can do stuff, it's just the expectation and the time courses are a little different. Also more aggressive treatment upfront generally rewards with better odds of coming off of therapy. So for example, in the case you say we're going to just do steroids. Three years out still on steroids, still with a little bit of disease, now you decide to do more aggressive treatment. You would've been better off starting sooner rather than waiting out for it. It'll be easier to achieve that remission and more likely to have a better outcome.

Dr. Kyle Amber: Then another thing is the role of maintenance infusions. This is controversial and really a lot of variability between physician practices. Basically, if I give two doses of Rituximab and then do absolutely nothing, there is a certain percentage of patients who will stay in remission, not have the disease come back. Also there's a large percentage who either that won't be enough or the disease will come back within two years. It sort of again, goes to how more aggressive upfront, better rewards in the future. If you say three infusions and a 30% chance of the disease not coming back, which I don't want to say is a made up number, but there's so much variability between studies that it's sort of somewhere in there. Versus eight infusions over the course of several years increase that odds to 60 to 70%. Is it worth it? I would generally say yes, because I really don't want people ever going on steroids again and having a major flare up and restarting this whole process. That's my perspective. But when people say, you don't need a maintenance infusion, you're in remission, we'll play it out. That's sort of that risk benefit thought process that's involved in there. It's hard to say if there's really a right or wrong. If we do more, you'll probably have better odds, are those odds worth it? Obviously it's individual dependent. Another thing is if you flare up again, can you tolerate another round of steroids, et cetera? So for example, people who have really severe adverse reactions to steroids, muscle problems, eye problems, bone fractures, et cetera. I view those people and I'm like, I cannot afford to have this patient flare back up and need to go through that again. I have no wiggle room. If they need high dose steroids and they can't eat, what do I do? Their muscles had toxicity last time. Another thing is blood testing to predict relapse rates. It can be helpful. Generally speaking, good labs, so low levels of these antibodies equals a higher chance of

remission, less chance of relapse. But it's a correlation. I've seen plenty of people whose blood work looks perfect and their skin looks terrible and vice versa. So it's one of those that I view more during the time point of treatment. If you treat a patient for a certain number of years without disease activity, it is a little more helpful than the blood, but certainly if the blood looks good, it makes you feel a little bit better about things.

Dr. Kyle Amber: The other thing is considering all of the other factors and sort of managing the person, not the disease. There's ways that I think are the most “effective” for treating the disease, but that doesn't mean it makes the most sense. Generally speaking, the disease affects the skin and mucosa, but the treatments affect everything else. So you have to balance that factor. And there's a huge mental health burden of PV that has to be considered. Steroids can cause sleep disturbance, anxiety, depression, blood sugar issues, blood pressure, bone mineral density and that requires sometimes a medication of its own just to prevent bone breakdown. Stomach ulcers and reflux, those can get worse with smoking. Taking large amounts of ibuprofen, et cetera and sometimes we have to add a therapy for that with those risk factors. Then the rare side effects that I alluded to like steroid toxicity or fractures in the hip. Those require rapid tapering of the steroids really, even if the disease is not going so well. We basically say I'd rather have some pemphigus activity than have muscle toxicity. It’s a balancing act. Again, works quickly, terrible side effect profile. Rituximab works slowly with less off-target side effects. Basically, it's very specific in what it does. Yes it is immunosuppressive and increases risk of infection, but it kills one cell. It really leaves the other cells alone and because of that you don't get the off target things like blood pressure, blood sugar issues, all of those. You can't get post infusion fatigue, myalgia. For IVIg, headaches, fatigue, blood clots, and then just frequency of treatments is usually the more frustrating part because it's just a lot of treatment.

Dr. Kyle Amber: So I really think it's important to manage all of these things to manage the person, not the disease. I think you can pick a treatment protocol that says 90% of patients will be in remission and is that the right treatment protocol for that individual? It depends, sometimes it is, but you have to manage all of those risk factors and side effects. That's an important thing, is basically to let us know as those side effects occur, because there's sometimes different ways of doing things that might not be optimal from treating the disease but maybe optimal for preventing other issues that are coming up. Just other considerations of things that come up sometimes in pemphigus fairly commonly that I thought worth mentioning. Herpes virus infections, people often assume I didn't have a cold sore, I don't have a history of cold sores or general herpes, so that's not affecting me. That's pretty far from the truth. One of the reasons we don't use blood work for diagnosing herpes or at least shouldn't is, up to 90% of

the population has been exposed to herpes virus. Most people have had it, they just don't know they have it. And the reason this becomes important is herpes virus flares can flare up pemphigus, which can then get infected and then the pemphigus gets worse and then things spiral out of control. It's not really the type of situation where I look at somebody and know they have it. There's a few studies where, if you swab hundreds and hundreds of spots, eventually you'll find it on one. So I have a very low threshold for treating herpes virus infections. The side effect profile of the medication is pretty much nothing. The way I view it, it's almost as close to zero risk as you can get from a medication with the plus side of sometimes that can really allow you to come off of the steroids. I've had numerous patients with oral pemphigus who, you put them on what you think the "right dose" of steroids is. You say, okay, based on their weight and disease severity, 80 milligrams should work. Nothing happens. You start treatment for herpes virus and within two weeks they're completely cleared up despite the fact you were going up on steroids. So that's one factor. Another one is esophageal involvement. Unfortunately pemphigus can involve the esophagus causing throat irritation, pain with eating. You have to consider common things. Reflux is going to be much more common, but unfortunately, usually you can have both. So you treat one and then see how it goes. So that's just something to consider in terms of symptoms. Then yeast infections can occur with immunosuppression or oral antibiotics. These can be vaginal or oral yeast infections. So it's just important to let us know.

Dr. Kyle Amber: This is just one thing that's come up over my time doing this is residual oral sensitivity. I find about 20% of patients will complain about this. After everything is done, they're off of prednisone, they haven't had disease activity, patients will feel like a blister wants to arise. Blood work may be negative, no blisters ever seen and it's really a sensory thing. I don't see an association with these patients and increased risk of relapsing. I don't know if there's a neurologic sensitivity or a PTSD of the mouth. Escalation of therapy just based on that symptom really has to be weighed with the risk because if that's not going to progress into a disease flare, is it worth, for example, starting Rituximab? In my experience, generally speaking, it's a symptomatic thing that doesn't really match, but I do see it quite frequently.
So I wanted to mention that.

Dr. Kyle Amber: Lastly, pemphigus is an autoimmune blistering disease caused by antibodies that attack the surface of the skin. Those are called keratinocytes. And the treatment really revolves around stopping those skin cells from fragmenting, that's the acute treatment. Then decreasing these bad antibodies from developing and that's more of the chronic treatment. The thing I can't ever highlight enough is pemphigus is treatable. It's just really an issue of selecting the right treatment protocol, weighing all of those things and finding what works best all together

for the person, the disease, et cetera. I always want to highlight that more than anything because I think what gets lost is, I can talk of the nitty gritty of do we do three versus five? But really at the end of the day, we should be able to get people almost all off of steroids and clear, otherwise we need to find something else that we're doing. So with that, I leave with questions and I'm happy to take any of those.

Becky Strong: Wow Kyle, thank you so much for the great overview. I learned a lot during your presentation, so thank you. We had an interesting question, and I'm going to start off with this one. Somebody was wondering, how was pemphigus 30 or even 50 years ago diagnosed? Was it previously diagnosed as another disease?

Dr. Kyle Amber: Now you're testing me on the history of dermatology. I believe even 50 years ago they were still doing direct immunofluorescence. They didn't have the quality of blood tests that they had before, but you were still able to diagnose it with direct immunofluorescence. It's actually been known for over, I believe it's been over about almost 120 years of being described. And actually, even in the veterinary literature, there's some too because dogs and cats can get pemphigus, as a fun fact. Some early observations were in that as well.

Becky Strong: Great, thank you. Gail had mentioned in the comment that something that they've noticed in the UK is that they have a lot of blood bruises, excessive bleeding or thin skin and GI problems and not everybody is on steroids. Is that something that's common with pemphigus?
Dr. Kyle Amber: Upper gastrointestinal such as the throat we can see. There are some described cases of gastrointestinal involvement, which are quite uncommon. As far as bruising, generally the biggest reason I see that is steroid usage. Steroids can increase bruise ability and that includes topical steroids as well. Now the skin fragility with pemphigus can leave, pemphigus is notorious for leaving very dark spots behind that are just completely out of proportion to other dermatologic problems. Some people will describe those as bruises even though they're called post-inflammatory hyperpigmentation so a slightly different thing, but that's a very telltale sign of pemphigus.

Becky Strong: That makes a lot of sense. Thank you. What are the chances of the mouth lesions changing into cancer if you've had them for a few years?

Dr. Kyle Amber: Generally speaking, we think relatively low. There's a lot of literature in lichen planus, which is a different oral disease in terms of risk of developing cancer with longstanding

ones. Pemphigus is not very inflammatory. So when we talk about chronic oral lesions becoming cancer, we really talk about chronic inflammation. Chronic inflammation is a huge risk factor for cancer development. Pemphigus is more, again, these fragmented cells. Those can become inflamed, sometimes long-acting lesions will be inflamed. So there may be an increased risk, but generally speaking, that's not really my thought with a chronic one so much it is really not a strong association.

Becky Strong: Great. What role does the gut biome play in treating pemphigus?

Dr. Kyle Amber: That's a good question. So it depends who you ask, it's either 100% or 0% depending. There's very little data. We know that for example, stool bacteria in patients is going to be a little bit different. But what's unclear is ,first of all what do you do about it? Probiotics doesn't seem to fix everything. We know that there's a huge interaction of the microbiome around us and within us. There's even a microbiome on the skin, for example, which plays a big role and that's coming more into detail in pemphigoid. So there is presumably a role. It is probably a small to a moderate contributory factor where I doubt that fixing that would undo it because why do antibiotics not magically clear everybody up? They seem to have a small beneficial effect, but there's something there we just don't quite know what to do about it and how it actually will impact patients.

Becky Strong: Great, thank you. Carlos asked the question that I was waiting for, is there any research that showed that either Covid or the Covid vaccine can cause pemphigus?
Dr. Kyle Amber: So cause is always a careful word there. The problem is, cause implies one thing leads to another. We see a ton of Covid. Covid itself is a very immunogenic disease so we see a lot of autoimmune diseases presenting after Covid and also the vaccine too. Clinical experience, I'd say yes, I see an increased risk with both the infection and vaccine. That is not to say causative. If you had 99 out of a 100 risk factors and you got Covid that was your 100th, that pushed you over, did it cause it? You would perceive it as that but the hundreds of other things that went wrong, you wouldn't. There have been studies that sort of negate that clinical observation that a lot of us have that basically show patients with pemphigus, they get a vaccine, nothing happens to their blood levels. If you look at a population level, technically no increase. So I'd say my observation, yes, the data says no, there's a little bit of a disconnect, but we do know Covid itself really stimulates the immune system quite strongly.

Becky Strong: Great, thank you. I'm going to combine a couple questions here. It's about Rituximab. One is how long does it take Rituximab to work? You kind of touched on that during the presentation, and then is there an age limit for Rituximab?

Dr. Kyle Amber: Generally if you do nothing, seven months or so is the optimal time. And keep in mind pemphigus and pemphigoid are going to be a little different, so I'm going to really stick on pemphigus. That is not to say it does 0 to a 100 magically between month 6.5 and 7. The problem with Rituxan is it's very unpredictable. It should take a while to work. Yet there are patients who after six weeks are doing great and I'm like, well, that's faster than I expected. So anywhere from 6 to 12 weeks is when I expect maybe it will be doing something. By about 3 months is, in my head when I'm saying, okay, it should be doing something, I can pick up the speed of tapering steroids, for example, because it should be where the curves intersect. But to actually reach full effect is quite slow. So I'd put it around 7 months.

Becky Strong: Great, thank you so much. Doreen is asking, how often would you suggest somebody get blood work?

Dr. Kyle Amber: So it depends a little bit on what you're on and what risk factors you have. I think this is just a point in medicine that I try to teach my residents is, don't get a test where you don't know what you're looking for because you get information and when you have a slight lab abnormality that's not actionable now what do I do with that? For Rituxan, you really are not checking much. You need a hepatitis test before starting. Generally it's recommended to do it yearly, but there's some risk factors that we don't necessarily need to repeat it. With routine blood tests, there's nothing I'm looking for. I expect it to drop one of the cells a little bit. So I see that and I say, okay, it did what it did. With steroids sometimes I'm worried about diabetes, that would be just one that I'd look for. But I tend to be on the side as a minimalist in most of these treatments because the drugs don't actually cause problems that you can pick up in blood work. Mycophenolate if on, that's usually about 3 months because that can cause problems and there's stuff that we're looking for. Even though I say in clinical experience, I really don't see as much, but the book says to do every 3ish months, so I do every 3 months. But my principle just in medicine I think is, don't just check for the sake of checking. Check because there's something you're worried about at a certain time. And with Rituxan for example, we just don't really see that much.

Becky Strong: Great, thank you. John is asking, do you have any suggestions for managing PV on the scalp?

Dr. Kyle Amber: It depends a lot. So basically let's say it's just scalp as an early pemphigus presentation, even if it's just in one area, I think you have to treat these things from the inside out. I'm really not a big fan of topical therapies because I think you're making antibodies from the inside that are attacking the skin and you're trying to put a bandaid on the outside to fix it. That said, topical steroids can be helpful sometimes to speed things up. If it's a very chronic stubborn spot in the scalp, a lot of times we inject those with a steroid and it tends to work quite well and sometimes inject Rituxan if the steroids aren't quite working. But it depends if it's really that early phase where it behaves just like pemphigus anywhere or that late phase where it's just that chronic stubborn lesion.

Becky Strong: Great. And you kind of touched on this in that answer, do you feel that a steroid rinse, like a dexamethasone rinse is helpful?

Dr. Kyle Amber: Helpful, yes. Is it ever enough to get people to exactly where they'd want with pemphigus generally speaking, no.I use a dexamethasone rinse in patients who have very diffuse disease where say there's 50 spots. Whereas if somebody has one or two spots, that's where I use clobetasol gel to really hammer those spots. And I think it can help speed things up but to do that without doing anything else, the expectation is it probably won't go well. In say, mild to moderate oral disease, you can do that, start Rituximab and cross your fingers that you buy yourself 7 months of time with the topical regimen to avoid oral steroids. We do that plenty and it can work. But to just do the oral steroids, the exception is sometimes we'll see somebody who has just 10 years of one stubborn spot that's kind of an outlier so I ignore that one. But in general I think it's usually not enough.

Becky Strong: Great. Thank you. Athena asks, can oral pemphigus vulgaris cause gum bleeding even if there are no sores present?

Dr. Kyle Amber: Yeah, absolutely. An important thing with pemphigus that I didn't really touch on so much in clinical findings is, just because you see a blister in one area doesn't mean the rest of the skin is normal. There's a test we do in the clinic called the Nikolsky sign where basically you push really, really hard down on the skin and if the skin sort of comes off like a ribbon, you say yikes, the disease is still active. And we do that for example, if I think somebody is able to come off of steroids, but I'm like, they haven't had new blisters, I'm worried they still have some activity. If you do that and it comes off, you're like, okay, I cannot go any lower on steroids or that's all going to become active disease. And the same thing is true in oral disease.

So basically you have fragility. So if you were to scrub really hard, you could induce a microscopic blister and then that causes bleeding. That just tells you there's some activity still.

Becky Strong: Great, thank you. You had talked about the dark spots before that you can sometimes get, is there a good chance for these dark spots to go away or will they remain as you said, they look like bruises?

Dr. Kyle Amber: They do go away almost always, but with a lot of time and a lot more time than people want to wait, somewhere along the lines of 2ish years. I don't recommend bleaching regimens and things like that. It doesn't work unfortunately. The pigment is very deep in the skin and so unfortunately there's not a great fix other than fix the pemphigus so that doesn't happen. But the natural course of those is yes, they do go away they're just incredibly slow. So for somebody with darker skin types, who's used to if you get a bug bite and you get a dark spot. The dark spot lasts for a couple months and goes away. You have to multiply that by about 5 to 10 in terms of the duration just because it's a different amount of inflammation or damage to the skin that's causing that dark spot.

Becky Strong: Somebody has submitted a question and it says that they have stubborn lesions in two places in their mouth and that they're still there the past 3 or 4 years even after taking medicines like Rituximab. Is there anything that can be done to get those to go away?
Dr. Kyle Amber: Yeah, so injecting them. So generally my feeling is you have to keep somebody on therapy so that those don't stimulate the immune system to restart the process again, but that's the background. That still doesn't answer the question, how do we get rid of those ones? That's usually where injection of a steroids works. In my experience, about 60% of the time of injecting it in there. I have had some luck with injecting Rituxan directly into those spots. Getting insurance to approve that and whatnot, that's always a fun process to do. But it can work because again, those really stubborn areas, think of them, like a little mini immune system in the skin itself that's independent of the rest of your body, so you have to kind of treat it like that.

Becky Strong: Great. So I'm going to combine the next couple of questions. Do you think that any diets keep pemphigus in remission and are there any nutrient considerations to think about when you have this disease?

Dr. Kyle Amber: So this is either a really long question or short. I would say the short answer is don't bank on diet for helping things. The slightly more nuanced answer is we did a study

together with IPPF on patients and diet, and there's certain foods such as hard foods like deep fried foods, citrus and spicy foods that patients did report increased risk of flarings and discomfort. But there's also a common sense element there that if you have active oral erosions and you're using all of those things that would do it. There didn't seem to be any great trends. When we look at food, 15% of anybody you ask will say, oh, this food causes me some arbitrary problem, which is subjective. So setting that as a threshold, there's nothing that seemed to stand out as making a big difference. There are some studies on garlic, onions and red wine, sorry for the red wine folks that can increase the keratinocyte fragmentation.
So if you take a patient's blood with pemphigus, add it to skin cells and add those things, it can increase fragmentation. There was this nice case where they said this person stopped eating garlic and their pemphigus got better and then they started garlic and it got worse. It sounds very nice and appealing. The reality of it is, again, these are small things, so I don't believe that you're going to make a substantive difference. I think basically if you notice something makes it worse, it's real. If you notice something makes it better when you stop it, that's also probably real. But at the same point in time, I don't think there's a generalizable thing that I can tell you that works uniformly for the disease. I think those 3, the garlic, onions, et cetera, we have some evidence for, but it's going to be pretty minor. I try to say the short answer is don't worry about the food, that's not the reason.

Becky Strong: Lisa is asking what is the best treatment plan for somebody with type one diabetes? If you have type diabetes, are high dose steroids still recommended?

Dr. Kyle Amber: This is always a balancing act and it is nuanced. The problem is, in general, we don't like to use steroids with diabetes. It will cause the sugar levels to go up, but insulin will cause those levels to go back down. So a lot of times it's a matter of just adjusting the insulin levels. When I see the book that says, you should avoid using steroids in these patients with diabetes, I think to myself, do you think I enjoy using steroid? I don't give them willy nilly. It's basically because someone's lost 30 pounds and can't eat. I got to do something. If somebody's 50/50 and they're on the more mild side and it's like, do I want to tough it out and wait the X long time for Rituxan? That would be a factor. But it's just another complexity of the therapy. But I think you treat the person and don't say, I can't treat them because if they have this then they lose 50 pounds weight, I don't think that's fair.

Becky Strong: Great. Thank you. Are there any studies on using red light therapy to ease lesions?

Dr. Kyle Amber: This is a good question. So every year there's usually something trending like apple cider vinegar. Red light therapy is the thing of this year. I feel like that for some reason I've gotten a lot of questions about. Unfortunately there's not a lot of data for it and there are a lot of people selling red light therapy so there's always that balancing act of things. We do know pemphigus is a light sensitive disease. So for example, ultraviolet light can increase the sensitivity of the cells to shrivel up. So the short answer is, I don't know. The other answer is, I wouldn't necessarily try messing around with it because I don't really know. But I also think it is one of those, the fad of 2024 and late 2023.

Becky Strong: Great. Thank you for that. Is something like a bleach bath considered an effective treatment to help remove pain when you have pemphigus vulgaris?

Dr. Kyle Amber: Not really. It's usually going to be pretty irritating. So I am not a fan of bleach baths just because the data is still mixed. Eczema is where we have the most data and they used to be routinely recommended. It's really for removing bacteria that lives on the skin, which is thought to contribute to the disease, and in pemphigus we don't think that. It can potentially decrease risk of infection, but it may also potentially be really irritating and cause issues. In other countries where they use banana leaves, which have been shown to have some effects and pain relief for the individual lesions. But generally speaking, something like the thickest, goopiest moisturizer is usually going to be helpful and treating it from the inside so that it heals itself quickly.

Becky Strong: Great, thank you. Alpa is asking, how long should you take only oral medications before considering something like Rituxan?

Dr. Kyle Amber: My opinion, and I realize that this is just my opinion, is I immediately am planning plan B the second I start plan A. The only exception would be if somebody is a 100 years old with a severe heart issues, dementia, et cetera, very poor prognosis. Then you say, maybe I can give them a dusting of prednisone and that'll keep the disease under control. But the natural course of the disease is it wants to stick around. If I start plan A, which is generally steroids, what am I doing? What am I accomplishing? I always use steroids as the bridge to get you off of steroids. So I'm always starting plan B immediately with plan A. And given that Rituxan works so much better than the oral immunosuppressants, I really don't see a reason to start those and wait. Just get people moving in the right direction, get them off of steroids as soon as possible.

Becky Strong: Great. William is asking, is Plaquenil an effective treatment for pemphigus?

Dr. Kyle Amber: Short answer, no. It tends to be a very popular treatment that I see in pemphigus foliaceus preferred by people who do not treat a lot of pemphigus foliaceus unfortunately. I'm not really sure why, but generally speaking it is quite ineffective. The safety profile is really nice, so that's why a lot of people like to add it, but it tends to be in our toolbox of treatments when we are not really sure what to do. We know there's an immune issue going on, so we say, let's try Plaquenil. But it really doesn't work very well in pemphigus, at least.

Becky Strong: Great, thank you. We've also had some questions asking, do you take patients out of state and are you accepting patients into your practice now?

Dr. Kyle Amber: Yes, I'm happy to. I think you have my email address. Usually I can get people in. This is generally going to be true with most people with autoimmune blistering diseases and things with a fair amount of acuity is, if something's going bad, reach out. Even though our wait list is like 6 months routinely, I usually can get somebody in within about 2 weeks or so. With out of state, one thing that's unfortunately frustrating is the Covid emergency laws change, so now we can see people out of state. We just can't do telehealth out of state anymore, and that unfortunately changed in 2023.

Becky Strong: Well, thank you so much. This has been an amazingly quick hour, and I appreciate the time and the preparation that you've put into today for our community. It was an amazing time, so thank you so, so much. Before I go today, I do have a few announcements. Since February is rare disease month, we plan on having weekly webinars pertaining to different parts of our journey with these diseases. Join us for our next webinar, and hopefully voice will be back by then on February 13th with our guest, Dr. Steven Davlouy, Associate Professor of Dermatology and Program Director at Wayne State University to discuss your mental health when you have a skin disease. Then on February 21st, Carly Flumer, patient advocate, will discuss narrating your story: advocating with a rare disease. You can scan the QR code on the screen and go to our website to register for each webinar. Please be sure to register for each webinar that you would like to attend.

Becky Strong: Next, do you want doctors and researchers to understand our diseases better? Do you wish there were more FDA approved treatments and better treatments available? Well, here's your chance to get involved and make those goals a reality. Please join the IPPF Natural History Study today. The Natural History Study is a patient registry sponsored by the National Organization for Rare Disorders (NORD) and the US Food and Drug Administration. Your information is private. The Natural history study does follow strict governmental guidelines to ensure patient information is protected. The IPPF will use your participation in the data to help

advance research, better understand the patient journey, find better treatments, and one day hopefully a cure. By sharing your journey and answering some questions, you directly affect the future of all people affected by pemphigus and pemphigoid.
So get involved today. Visit www.pemphigus.iamrare.org or scan the QR code on your screen and join today.

Becky Strong: Next, we'd like to thank everybody in our community for their continued generous support of the IPPF. Your donations help connect patients with support resources and disease experts and raise awareness. With your support we also share the patient experience with medical and dental professionals and students, advocate at the government level and promote research. You can scan the QR code on your screen or visit www.pemphigus.org/donate to donate today. You can help ensure that our programs are available for all of those who need them today and for many years to come. The IPPF also has virtual support groups across the country. If you're interested in attending a meeting, please check the IPPF'S event page to register for the meeting. We're also looking to expand our network, so if you would like to start a support group in your region, please contact me, Becky Strong at becky@pemphigus.org. It's a lot easier than it sounds to start a support group, and you can help connect others in your area with patients and their families. This call recording will be sent out with the survey following this call. Thank you for hanging with my bad voice. Goodbye.